REC'D 16 SEP 2005
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PCT

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

(Chapter II of the Patent Cooperation Treaty)

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference PCT-162	**FOR FURTHER ACTION** See Form PCT/IPEA/416	
International application No. PCT/ES2004/000188	International filing date *(day/month/year)* 30.04.2004	Priority date *(day/month/year)* 30.04.2003
International Patent Classification (IPC) or national classification and IPC A61K31/366, A61K31/22, A61K31/40, A61K31/404, A61K45/06, A61K31/00, A61P31/12, A61P31/18, A61K38/17		
Applicant CONSEJO SUPERIOR DE INVESTIGACIONES CIENTIFICAS		

1. This report is the international preliminary examination report, established by this International Preliminary Examining Authority under Article 35 and transmitted to the applicant according to Article 36.
2. This REPORT consists of a total of 14 sheets, including this cover sheet.
3. This report is also accompanied by ANNEXES, comprising:
   a. ☐ *sent to the applicant and to the International Bureau)* a total of sheets, as follows:
      ☐ sheets of the description, claims and/or drawings which have been amended and are the basis of this report and/or sheets containing rectifications authorized by this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions).
      ☐ sheets which supersede earlier sheets, but which this Authority considers contain an amendment that goes beyond the disclosure in the international application as filed, as indicated in item 4 of Box No. I and the Supplemental Box.
   b. ☐ *(sent to the International Bureau only)* a total of (indicate type and number of electronic carrier(s)) , containing a sequence listing and/or tables related thereto, in computer readable form only, as indicated in the Supplemental Box Relating to Sequence Listing (see Section 802 of the Administrative Instructions).

4. This report contains indications relating to the following items:

☒	Box No. I	Basis of the opinion
☐	Box No. II	Priority
☒	Box No. III	Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
☒	Box No. IV	Lack of unity of invention
☒	Box No. V	Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
☒	Box No. VI	Certain documents cited
☐	Box No. VII	Certain defects in the international application
☐	Box No. VIII	Certain observations on the international application

Date of submission of the demand	Date of completion of this report
26.01.2005	15.09.2005
Name and mailing address of the international preliminary examining authority: European Patent Office - P.B. 5818 Patentlaan 2 NL-2280 HV Rijswijk - Pays Bas Tel. +31 70 340 - 2040 Tx: 31 651 epo nl Fax: +31 70 340 - 3016	Authorized Officer Cielen, E Telephone No. +31 70 340-

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No.
PCT/ES2004/000188

Box No. I Basis of the report

1. With regard to the **language**, this report is based on the international application in the language in which it was filed, unless otherwise indicated under this item.

   ☐ This report is based on translations from the original language into the following language , which is the language of a translation furnished for the purposes of:
   - ☐ international search (under Rules 12.3 and 23.1(b))
   - ☐ publication of the international application (under Rule 12.4)
   - ☐ international preliminary examination (under Rules 55.2 and/or 55.3)

2. With regard to the **elements*** of the international application, this report is based on *(replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report)*:

Description, Pages

1-53 as originally filed

Claims, Numbers

1-29 as originally filed

Drawings, Sheets

1/9-9/9 as originally filed

☒ a sequence listing and/or any related table(s) - see Supplemental Box Relating to Sequence Listing

3. ☐ The amendments have resulted in the cancellation of:
   - ☐ the description, pages
   - ☐ the claims, Nos.
   - ☐ the drawings, sheets/figs
   - ☐ the sequence listing *(specify)*:
   - ☐ any table(s) related to sequence listing *(specify)*:

4. ☐ This report has been established as if (some of) the amendments annexed to this report and listed below had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).
   - ☐ the description, pages
   - ☐ the claims, Nos.
   - ☐ the drawings, sheets/figs
   - ☐ the sequence listing *(specify)*:
   - ☐ any table(s) related to sequence listing *(specify)*:

* *If item 4 applies, some or all of these sheets may be marked "superseded."*

Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application,

☒ claims Nos. 1-7 (partially), 8-15 (entirely), 16-17 (partially), 18 (entirely), 19 (partially), 20-29 (entirely)

because:

☐ the said international application, or the said claims Nos. relate to the following subject matter which does not require an international preliminary examination (specify):

☐ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. are so unclear that no meaningful opinion could be formed *(specify)*:

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

☒ no international search report has been established for the said claims Nos. 1-7 (partially), 8-15 (entirely), 16-17 (partially), 18 (entirely), 19 (partially), 20-29 (entirely)

☐ the nucleotide and/or amino acid sequence listing does not comply with the standard provided for in Annex C of the Administrative Instructions in that:

the written form	☐	has not been furnished
	☐	does not comply with the standard
the computer readable form	☐	has not been furnished
	☐	does not comply with the standard

☐ the tables related to the nucleotide and/or amino acid sequence listing, if in computer readable form only, do not comply with the technical requirements provided for in Annex C-*bis* of the Administrative Instructions.

☐ See separate sheet for further details

Box No. IV Lack of unity of invention

1. ☒ In response to the invitation to restrict or pay additional fees, the applicant has:
   - ☐ restricted the claims.
   - ☐ paid additional fees.
   - ☐ paid additional fees under protest.
   - ☒ neither restricted nor paid additional fees.

2. ☐ This Authority found that the requirement of unity of invention is not complied with and chose, according to Rule 68.1, not to invite the applicant to restrict or pay additional fees.

3. This Authority considers that the requirement of unity of invention in accordance with Rules 13.1, 13.2 and 13.3 is

   ☐ complied with.

   ☒ not complied with for the following reasons:

   see separate sheet

4. Consequently, this report has been established in respect of the following parts of the international application:

   ☐ all parts.

   ☒ the parts relating to claims Nos. 1-7, 16, 17, 19 (all partially) .

Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	-
	No:	Claims	1-7, 16, 17, 19
Inventive step (IS)	Yes:	Claims	-
	No:	Claims	1-7, 16, 17, 19
Industrial applicability (IA)	Yes:	Claims	1-7, 16
	No:	Claims	

2. Citations and explanations (Rule 70.7):

   see separate sheet

Box No. VI Certain documents cited

1. Certain published documents (Rule 70.10)

   and / or

2. Non-written disclosures (Rule 70.9)

   see separate sheet

Supplemental Box relating to Sequence Listing

Continuation of Box I, item 2:

1. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application and necessary to the claimed invention, this report has been established on the basis of:

   a. type of material:

   ☒ a sequence listing

   ☐ table(s) related to the sequence listing

   b. format of material:

   ☒ in written format

   ☒ in computer readable form

   c. time of filing/furnishing:

   ☒ contained in the international application as filed

   ☐ filed together with the international application in computer readable form

   ☒ furnished subsequently to this Authority for the purposes of search and/or examination

   ☒ received by this Authority as an amendment on

2. ☒ In addition, in the case that more than one version or copy of a sequence listing and/or table(s) relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

3. Additional observations, if necessary:

Re Item III

Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

III.i. Claims 17 and 19 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(I) PCT).

III.ii. This application does not meet the requirements of Article 5 and 6 PCT, because claims 1-7, 16, 17 and 19 are not clear, nor sufficiently supported and the invention is not sufficiently disclosed by the description.

(a) Present claims 1, 5, 7, 16, 17 and 19 relate to compounds which actually are not well-defined. The use of the definitions "or derivative thereof", "or an analogue thereof" in the present context is considered to lead to a lack of clarity within the meaning of Article 6 PCT. The lack of clarity is such as to render a meaningful complete search impossible.

(b) In addition, present claims 1-5, 7, 16, 17 and 19 relate to a compound defined by reference to a desirable characteristic or property, namely "a protein isoprenylation inhibitor", "an inhibitor of geranyl geranyl pyrophosphate synthase", "an inhibitor of Rho activation", "a statin" and "agents capable of inhibiting protein isoprenylation". The claims cover all compounds having this characteristic or property, whereas the application provides support within the meaning of Article 6 PCT and disclosure within the meaning of Article 5 PCT for only a very limited number of such compounds. In the present case, the claims so lack support, and the application so lacks disclosure, that a meaningful search over the whole of the claimed scope is impossible. Independent of the above reasoning, the claims also lack clarity (Article 6 PCT). An attempt is made to define the compounds by reference to their pharmacological profile. Again, this lack of clarity in the present case is such as to render a meaningful search over the whole of the claimed scope impossible.

(c) Moreover, present claims 1-7, 16, 17 and 19 relate to the treatment of diseases which actually are not well-defined. The use of the definitions "a retroviral infection genetically related to HIV" in the present context is considered to lead to a lack of clarity within the meaning of Article 6 PCT. It is not fully possible to determine the diseases for which protection might legitimately be sought. The lack of clarity is such as to render a meaningful complete search impossible.

(d) Consequently, the search has been carried out for those parts of the claims which appear to be clear, supported and disclosed, namely those parts relating to the

statins specifically mentioned in claim 6 and the real and defined diseases specifically mentioned in claims 1, 16, 17 and the description par [0032] and par. [0069], namely HIV, AIDS and Ebola, with due regard to the general idea underlying the application.

(e) It appears that the claim dependency is not correct for the following claims: It appears that claim 18 should be dependent on claim 17 and claims 20-27 on claims 18-19 and following claims. Furthermore, it appears that claims 10-11 and 13 should only be dependent on claim 8. It is not clear on which claim claim 12 should depend.

No opinion of the International Search Authority will be given in respect of subject-matter which is not covered by the search report (Rule 66.1(e) PCT) (see also items **IV** and **V.i**).

Re Item IV

Lack of unity of invention

The present application lacks unity of invention in the sense of Rule 13.1 PCT for the following reasons:

The problem to be solved by the present application is the provision of alternative medicines for the treatment of a HIV infection, a retroviral infection genetically related to HIV, or AIDS.

The proposed solutions are (i) the use of a protein isoprenylation inhibitor, preferably a statin, or (ii) the prevention of the accumulation of HIV receptors in raft domains by providing a non-raft mutant cytokine receptor.

Thus, in the context of the alleged invention, the use of compounds that inhibit the ability of HIV and related viruses from exploiting host cell raft domain structures as means of entering the cells and propagating additional virus particles is the alleged contribution over the prior art and the special technical feature which may, a priori, unify the plurality of different inventions (see description, p. 19, par. [0042]; p. 26, par. [0074]).

The use of compounds that inhibit the ability of HIV and related viruses from exploiting host cell raft domain structures has been previously disclosed.

See e.g. EMBO reports, 1(2), 190-196, 2000 (Mañes) (D7), which discloses that membrane rafts may be a target for new strategies to prevent/block HIV-1 infection. Disruption of the cell membrane rafts by cholesterol depletion inhibits the entry by HIV-1 (Abstract; p. 194, left-hand column, par. 1).

Gower et al. disclose in Antimicrobial Agents and Chemotherapy, 45(4), 1231-1237 (2001) (D8) that lovastatin inhibits lipid rafts, which play an important role in HIV-1 (p. 1236, left-hand column, par. 2).

US2002142940 (D1) teaches that inhibitors of HMG-CoA reductase and isoprenylation, such as geranylgeranyl transferase inhibitors, can be used to inhibit a cellular entry receptor for a number of viruses which utilise the RhoA receptor, including HIV-1 and Ebola virus (p. 1, par. [0010]-[0011]; p. 3, par. [0028]-[0029], [0031], [0038]; p. 4, par. [0049]-[0050]; p. 5, par. [0057]-[0058]; p. 6, par. [0069]-[0071], [0075]; p. 8, par. [0093]; claims 1, 2, 5, 7-10, 13-15, 21, 25, 27-28, 33-35, 41-46). Statins, such as lovastatin, pravastatin, simvastatin, fluvastatin, atorvastatin and mevastatin, can be used as the HMG-CoA reductase inhibitors; lovastatin also inhibits protein isoprenylation (p. 5, par. [0064]-[0067]). The compounds can be used alone or in combination with a nucleoside analog, a non nucleoside reverse transcriptase inhibitor or an inhibitor of virus entry (p. 6-7, par. [0077]-[0081]).

WO0047196 (D2) discloses the use of a statin, such as mevastatin, lovastatin, pravastatin, and simvastatin for the treatment of viral infections, such as HIV (p. 1, lines 1-6; p. 1, line 33 - p. 2, line 7; p. 3, lines 28-37; p. 19, lines 9-18; examples 6, 9-15; claims 1, 4, 6-12, 15, 16). The compounds can be used alone or in combination with e.g. an anti-viral drug (p. 16, lines 7-21; p. 18, lines 17-22).

It is to be noted that even though US2002142940 and WO0047196 do not mention the involvement of raft domains, they disclose the idea to use statins for the treatment of HIV and related infections.

The fact that the disruption of raft domains may be involved in the treatment by statins of HIV and related infections reflects the mechanism underlying the treatment of the claimed diseases with the compounds of the present invention. Although the discovery of such a mechanism may be an important piece of scientific knowledge, it cannot be considered as a technical contribution to the art, since it still needs to be turned into a practical application in the form of a specified actual treatment of the pathological condition. In the present case, the specified actual treatment of the pathological conditions HIV and related infections was already disclosed in the prior art.

The idea to use compounds that inhibit the ability of HIV and related viruses from

exploiting host cell raft domain structures is not novel; it can therefore not fulfil the role of special technical feature in the sense of Rule 13.1 PCT. Therefore, no link exists between solutions (i) and (ii) as identified above.

In addition, since the use of a protein isoprenylation inhibitor, preferably a statin, either alone or in combination with other therapeutic agents, for the treatment of HIV infection has been previously disclosed (see e.g. US2002142940 and WO0047196), no further technical feature(s) can be identified which may be regarded as a "special technical feature" involved in the technical relationship between (a) the use of a protein isoprenylation inhibitor for the treatment of HIV infection and the use of a protein isoprenylation inhibitor in combination with further therapeutic agents for the treatment of HIV infection, and (b) between the use of a protein isoprenylation inhibitor in combination with anti-viral agents, raft-domain inhibitory agents, chemokine receptor modulatory agents, cholesterol reducing agents, protein prenylation reducing agents, Rho-A GTPase inhibitors and glycosphingolipid reducing agents.

Hence the International Authority considers that the following separate inventions or groups of inventions are not so linked as to form a single general inventive concept:

1. Claims 1-7, 16, 17, 19 (all partially)

The use of a protein isoprenylation inhibitor or of a pharmaceutically acceptable salt, solvate or derivative thereof for the manufacture of a medicament for the treatment of a HIV infection, a retroviral infection genetically related to HIV, or AIDS, wherein the protein isoprenylation inhibitor is not administered in combination with one or more therapeutic agents as defined in inventions 2-5.

2. Claims 1-8 (partially), 14-19 (partially), 20 (entirely), 22 (entirely), 27 (partially)

The use of a protein isoprenylation inhibitor or of a pharmaceutically acceptable salt, solvate or derivative thereof for the manufacture of a medicament for the treatment of a HIV infection, a retroviral infection genetically related to HIV, or AIDS, wherein the protein isoprenylation inhibitor is administered in combination with one or more antiviral agents, which are selected from the group comprising a HIV protease inhibitor, a non-nucleoside reverse transcriptase inhibitor, a nucleoside/nucleotide reverse transcriptase inhibitor, a CCR5 antagonist, an integrase inhibitor, a RnaseH inhibitor, nucleosides, nucleotides, protease inhibitors, pyrimidinones and pyridinones.

3. Claims 1-8 (partially), 10-12 (entirely), 14-19 (partially), 23-25 (entirely), 27 (partially)

The use of a protein isoprenylation inhibitor or of a pharmaceutically acceptable salt, solvate or derivative thereof for the manufacture of a medicament for the treatment of a HIV infection, a retroviral infection genetically related to HIV, or AIDS, wherein the protein isoprenylation inhibitor is administered in combination with one or more raft domain inhibitory agents or a chemokine receptor modulatory agent (other than a CCR5 antagonist).

4. Claims 1-8 (partially), 13 (entirely), 14-19 (partially), 26 (entirely), 27 (partially)

The use of a protein isoprenylation inhibitor or of a pharmaceutically acceptable salt, solvate or derivative thereof for the manufacture of a medicament for the treatment of a HIV infection, a retroviral infection genetically related to HIV, or AIDS, wherein the protein isoprenylation inhibitor is administered in combination with one or more cholesterol reducing agents, protein prenylation reducing agents or Rho-A GTPase inhibitors.

5. Claims 1-8 (partially), 9 (entirely), 14-19 (partially), 21 (entirely), 27 (partially)

The use of a protein isoprenylation inhibitor or of a pharmaceutically acceptable salt, solvate or derivative thereof for the manufacture of a medicament for the treatment of a HIV infection, a retroviral infection genetically related to HIV, or AIDS, wherein the protein isoprenylation inhibitor is administered in combination with one or more glycosphingolipid reducing agents.

6. Claims 28-29 (entirely)

A method of treatment of a mammal suffering from HIV, a retroviral infection genetically related to HIV, or AIDS by preventing the accumulation of HIV receptors in raft domains comprising providing a non-raft targeted mutant cytokine receptor.

As the Applicant has not had a search report drawn up on the other inventions, **the application will be prosecuted on the basis of the invention in respect of which a search has already been carried out, in other words the invention first mentioned in the claims, i.e. claims 1-7, 16, 17, 19 (all partially).**

Re Item V

Reasoned statement with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

V.i. (a) Attention is drawn to the fact that the present statement expressed as to novelty, inventive step and industrial applicability refers only to matter for which an International Search Report has been drawn up (i.e. only for statins specifically mentioned in claim 6 and the real and defined diseases specifically mentioned in claims 1, 16, 17 and the description par [0032] and par. [0069], namely HIV, AIDS and Ebola, with due regard to the general idea underlying the application).

(b) Present claims 17 and 19 involve compositions or substances in a method of treatment of the human/animal body. For the assessment of such claims on the question whether they are industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

V.ii. Reference is made to the following documents:

D1: US 2002/142940 A1 (GRAHAM BARNEY SCOTT ET AL) 3 October 2002 (2002-10-03)

D2: WO 00/47196 A (HOLLIS EDEN PHARMACEUTICALS IN) 17 August 2000 (2000-08-17)

D3: MAZIERE J C ET AL: "LOVASTATIN INHIBITS HIV-1 EXPRESSION IN H9 HUMAN T LYMPHOCYTES CULTURED IN CHOLESTEROL-POOR MEDIUM" BIOMEDICINE AND PHARMACOTHERAPY, ELSEVIER, PARIS, FR, vol. 48, no. 2, 1994, pages 63-67, XP000965739 ISSN: 0753-3322

D4: DATABASE BIOSIS [Online] BIOSCIENCES INFORMATION SERVICE, PHILADELPHIA, PA, US; December 2002 (2002-12), NALBONE GILLES ET AL: "[Pleiotropic effects of statins: Implications in the treatment of

cardiovascular diseases.]" XP002298999 Database accession no. PREV200300146776

D5: WO 93/24660 A (GLENN JEFFREY S ; UNIV CALIFORNIA (US)) 9 December 1993 (1993-12-09)

D6: WO 00/02558 A (LONCHAMPT MARIE ODILE ; PREVOST GREGOIRE (FR); SOD CONSEILS RECH APPLI) 20 January 2000 (2000-01-20)

D7: MANES SANTOS ET AL: "Membrane raft microdomains mediate lateral assemblies required for HIV-1 infection" EMBO REPORTS, vol. 1, no. 2, August 2000 (2000-08), pages 190-196, XP008036256 ISSN: 1469-221X

D8: GOWER T L ET AL: "Antiviral activity of lovastatin against respiratory syncytial virus in vivo and in vitro" ANTIMICROBIAL AGENTS AND CHEMOTHERAPY, (APR 2001) VOL. 45, NO. 4, PP. 1231-1237. PUBLISHER: AMER SOC MICROBIOLOGY, 1752 N ST NW, WASHINGTON, DC 20036-2904 USA. ISSN: 0066-4804., April 2001 (2001-04), XP008036221

V.iii. Article 33(2) PCT.

The present application does not meet the criteria of Article 33(1) PCT, because the subject-matter of claims 1-7, 16, 17 and 19 is not new in the sense of Article 33(2) PCT.

(a) Claims 1-4, 16 and 17 relate to the mechanism underlying the treatment of the claimed diseases with the compounds of the present invention. However, the mere explanation of an effect obtained when using a compound in a known composition, even if the effect was not known to be due to this compound in the known composition, cannot confer novelty on a known process if the skilled person was already aware of the occurrence of the desired effect. Even if the disruption of raft domains and/or interaction with protein isoprenylation by the compounds of the present invention is indisputably a pharmacological effect, it cannot in itself be considered a therapeutic application, nor can it render the known treatment of a specified pathological condition, in the present case the known treatment of HIV and related infections, novel.

Although the discovery of such a mechanism may be an important piece of scientific knowledge, it cannot be considered as a technical contribution to the art, since it still needs to be turned into a practical application in the form of a specified actual treatment of the pathological condition. In the present case, the specified actual treatment of the pathological condition HIV and related infections was already disclosed

in the cited prior art documents (see below).

Consequently, whatever the merit of the scientific teaching provided by the application regarding the mechanism of action of the claimed compounds, it is only the therapeutic effect of the medicament, i.e. treating HIV and related infections, which is relevant for the assessment of novelty and inventive step within the meaning of Articles 33(2) and 33(3) PCT.

(b) Attention is drawn to the fact that the scope of claim 16 for which protection is sought as it is worded is regarded as a so-called "first medical use". Claims drafted in this way are only allowable if no other medical use has been earlier disclosed. Consequently, any document disclosing a medical use of a composition comprising a compound of the present application will be novelty-destroying for the subject-matter of those claims.

(c) Document D1 teaches that inhibitors of HMG-CoA reductase and isoprenylation, such as geranylgeranyl transferase inhibitors, can be used to inhibit a cellular entry receptor for a number of viruses which utilise the RhoA receptor, including HIV-1 and Ebola virus (p. 1, par. [0010]-[0011]; p. 3, par. [0028]-[0029], [0031], [0038]; p. 4, par. [0049]-[0050]; p. 5, par. [0057]-[0058]; p. 6, par. [0069]-[0071], [0075]; p. 8, par. [0093]; claims 1, 2, 5, 7-10, 13-15, 21, 25, 27-28, 33-35, 41-46). Statins, such as lovastatin, pravastatin, simvastatin, fluvastatin, atorvastatin and mevastatin, can be used as the HMG-CoA reductase inhibitors; lovastatin also inhibits protein isoprenylation (p. 5, par. [0064]-[0067]). Therefore, the subject-matter of present claims 1-7, 16, 17 and 19 is not novel over D1.

(d) Document D2 discloses the use of a statin, such as mevastatin, lovastatin, pravastatin, and simvastatin for the treatment of viral infections, such as HIV (p. 1, lines 1-6; p. 1, line 33 - p. 2, line 7; p. 3, lines 28-37; p. 19, lines 9-18; examples 6, 9-15; claims 1, 4, 6-12, 15, 16). The compounds can be used alone (p. 16, lines 7-8). Therefore, the subject-matter of present claims 1-7, 16, 17 and 19 is not novel over D2.

(e) Document D3 discloses that lovastatin, a cholesterol synthesis inhibitor, reduces HIV replication in H9 human T lymphocytes at an early stage of the infection. The mechanism may involve an interference with the cellular metabolism requiring isoprenoids (Abstract; p. 63, right-hand column, par. 2; p. 65, right-hand column, par. 2 - p. 66, right-hand column, par. 1). Therefore, the subject-matter of present claims 1-7, 16, 17 and 19 is not novel over D3.

(f) Document D4 discloses that statins inhibit geranylgeranylpyrophosphate and that they are effective in HIV infection. Therefore, the subject-matter of present claims 1-7, 16, 17 and 19 is not novel over D4.

(g) Document D5 discloses the use of inhibitors of prenyltransferases for inhibiting

viral infection, e.g. of the nef protein of HIV (p. 1, lines 9-13; p. 3, lines 6-19; p. 9, lines 9-23; p. 10, lines 3-29; p. 13, lines 6-14; claims 1-2, 8-9). Therefore, the subject-matter of present claims 1, 7, 16, 17 and 19 is not novel over D5.

(h) Document D6 discloses the use of prenyltransferase inhibitors for the treatment of AIDS (p. 1, lines 1-7; p. 2, lines 17-20; claims 1, 10). Therefore, the subject-matter of present claims 1, 7, 16, 17 and 19 is not novel over D6.

V.iv. Article 33(3) PCT.

The present application does not meet the criteria of Article 33(1) PCT, because the subject-matter of claims 1-7, 16, 17 and 19 does not involve an inventive step in the sense of Article 33(3) PCT.

Even if novelty can be restored, the present application will very likely lack inventive step over each of D1-D6, which clearly teach the use of protein isoprenylation inhibitors, c.q. statins for the treatment of HIV and related infections.